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DRUG SAFETY

Statin-induced liver injury in an area endemic for hepatitis B virus infection: risk factors and outcome analysis

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AIMS

Statin-induced liver injury (SILI) is quite rare, but may be severe. Little is known about the impact of chronic hepatitis B infection (CHBI) on SILI. We aimed to investigate the risk factors and outcome of SILI, with special reference to its interaction with CHBI.

METHODS

Patients with SILI were recruited from our hospital, and three-to-one drug-matched controls were randomly selected. The clinical data of the patients were then compared.

RESULTS

A total of 108 patients with SILI and 324 controls were enrolled. The patients with SILI were both older and had a higher statin dose than the controls. There was no predilection of liver injury associated with the seven available statins. Among the SILI patients, there was no statistical difference between the baseline and peak liver enzyme tests, and latency and severity between hepatitis B carriers ($n = 16$) and non-carriers ($n = 92$). High dose of statin and age were the two independent risk factors of SILI (OR and 95% CI: 1.93, 1.08–3.35, $P = 0.025$, and 1.73, 1.07–2.80, $P = 0.027$, respectively). Permanent discontinuation of statin was noted in 50 (46.3%) patients with SILI due to severe SILI or recurrent hepatotoxicity after rechallenge of other statins.

CONCLUSION

High dose of statin and old age may increase patient susceptibility to SILI; however, CHBI and abnormal baseline liver tests are not risk factors of SILI. Nonetheless, SILI is still worthy of notice, because nearly half of the overt cases discontinued statin treatment due to severe hepatotoxicity in this study.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Statin-induced liver injury (SILI) is generally believed to be rare, but it may be severe and fatal.
- Previous studies suggest that statin can be safely prescribed to patients with chronic hepatitis C and fatty liver diseases.
- Little is known about the impact of chronic hepatitis B infection on SILI, and the outcome of overt SILI.

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WHAT THIS STUDY ADDS

- This case–control study has shown that high dose of statin and old age may increase patient susceptibility to SILI.
- Chronic hepatitis B infection and abnormal baseline liver tests are not risk factors of SILI.
- We still need to remain alert to the occurrence of SILI, because nearly half of SILI cases in this study discontinued statin treatments due to severe hepatotoxicity.

Introduction

Statins, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are the most widely used cholesterol lowing agents in the world. Although statins are usually well tolerated and safe, some adverse effects may occur in patients [1]. Overall, statin-induced liver injury (SILI) is the major safety concern of these drugs.

The incidence rate of SILI was estimated to be 27/100 000, according to a prospective study from Iceland [1]. Although SILI is rare, it may be severe and even fatal. Understanding the risk factors of SILI may help us to prevent or alleviate this potentially grave hepatotoxicity. A review of previous studies reveals that pre-existing liver diseases, such as chronic hepatitis C and non-alcoholic fatty liver disease, do not increase the risk of statin-related abnormality of liver tests [2–7]. Therefore, it is suggested that statins can be safely prescribed to patients with chronic liver disease.

Chronic hepatitis B is prevalent in Asia, and studies have shown that chronic hepatitis B infection (CHBI) may increase the incidence and severity of anti-tuberculosis drug-induced liver injury [8–10]. However, little is known about the impact of CHBI on SILI. Furthermore, clinical data and information about the outcome of patients with SILI are sparse. The aim of this study was to investigate the characteristics, risk factors and outcome of SILI in Taiwan, with special reference to the influence of CHBI on SILI.

Methods

Patients and controls

The overt SILI subjects were recruited from the computerized database of Taipei Veterans General Hospital of patients who were treated from 2008 to 2012. This hospital is one of the largest medical centres in Taiwan, with 2980 beds and 2.5 million outpatients annually. The following ICD-9 codes were used to choose potential patients with liver injury: 573.3 (drug/toxic hepatitis), 570 (acute and subacute necrosis of liver), 570.0 (hepatic failure, acute), 571.40 (chronic hepatitis, unspecified), 571.8 (other chronic nonalcoholic liver disease), 070 (viral hepatitis), and 070.3 (viral hepatitis B without mention of hepatic coma). To select the patients with SILI, the patients with possible liver diseases identified by the above-mentioned database were cross-searched for the following ICD-9 codes of hyperlipidaemia: 272 (disorders of lipid metabolism), 272.4 (hyperlipidaemia, unspecified), 272.2 (mixed hyperlipidaemia), 272.3 (hyperchylomicronaemia), and 272.0 (pure hypercholesterolemia). The potential SILI patients were surveyed individually. Three-to-one drug-matched controls were randomized and collected from the patients with the aforementioned ICD-9 code of hyperlipidaemia. The study was approved by the Institutional Review Board of the Taipei Veterans General Hospital (201012003IC).

The inclusion criteria for patients with SILI were: (1) patients with hyperlipidaemia and under the treatment of statin for at least one week; (2) patients having the data of baseline liver biochemical tests and at least twice followed-up data of liver tests within the first 4 months of drug administration; (3) patients having one of the following abnormal liver tests: the peak serum alanine aminotransferase (ALT) more than 5 times the upper limit of the normal value (ULN), the peak serum alkaline phosphatase (ALP) more than 2 times the ULN, or the peak serum total bilirubin more than 2 times the ULN [11]; (4) when the baseline liver tests were abnormal, the peak ALT was more than 5 times the baseline value, or the peak ALP was more than twice the baseline value; (5) abdominal sonogram examination of the patients revealed no evidence of obstruction of biliary tracts, malignant tumour, gallstone and biliary tract stone. The exclusion criteria of patients with SILI were: (1) incomplete clinical and laboratory data of patients; (2) no abdominal sonography examination after abnormal liver tests; (3) other causes that could explain the abnormality of the liver tests, such as chronic hepatitis C, alcoholic liver disease, autoimmune hepatitis, primary biliary cirrhosis, Wilson's disease, shock, sepsis; and (4) co-administration of potentially hepatotoxic drugs and other class of hypolipidaemic agents, such as ezetimibe, bezafibrate, fenofibrate and gemfibrozil. We excluded patients with chronic hepatitis C because hepatitis C infection is relatively rare in Taiwan, and we intended to focus on the interaction of CHBI with SILI. The CHBI was defined as the persistent presence of serum hepatitis B surface antigen for more than 6 months, according to criteria established by the World Health Organization.

The inclusion criteria of controls were: (1) patients with hyperlipidaemia and under statin treatment for at least three months; (2) patients with baseline liver biochemical tests (at least serum ALT) and follow-up liver tests within the first 4 months of drug administration; (3) less than twice the ULN of peak serum ALT, ALP and normal total bilirubin level in each liver function test. The exclusion criteria of controls were incomplete clinical and laboratory data.

Evaluation of risk factors and severity

The possible risk factors selected for comparison in this study were age, sex, body mass index (BMI), habitual alcohol consumption, renal function, diabetes mellitus (DM), baseline liver biochemical test, peak liver biochemical test, type of liver injury, latency (incubation period), name of statin, dose of statin, hypersensitivity features and CHBI status.

The estimated glomerular filtration rate (eGFR) was used to represent the renal function. An eGFR less than 60 mL min^{-1} 1.73 m^{-2} was regarded as abnormal renal function. Habitual alcohol consumption was defined as wine or spirit drinking at least 3 times per week for more than 5 years. BMI larger than 25 kg m^{-2} was regarded as overweight according the definition of the Centres for Disease Control and Prevention, Taiwan. A dose of statin was classified as high or low dose for each statin, according to the available two different doses of statins manufactured by the pharmaceutical companies.

Types of SILI were categorized according to the suggestion of the International DILI Expert Working Group [12]. Accordingly, SILI was regarded as 'hepatocellular' when the ratio of times of ULN of ALT/times of ULN of ALP ≥ 5, and as 'cholestatic' when the ratio was ≤2, and 'mixed' when 2 < ratio < 5.

The severity of the SILI was classified on a scale of 1–5 as proposed by the US Drug-Induced Liver Injury Network (DILIN) as follows: (1) mild: serum total bilirubin < 2.5 mg dL^{-1} and international normalized ratio (INR) < 1.5; (2) moderate: total bilirubin ≥ 2.5 mg dL^{-1} or INR ≥ 1.5; (3) moderate–severe: patients were hospitalized or prolonged hospitalization because of DILI; (4) severe: total bilirubin ≥ 2.5 mg dL^{-1} with one of the following: INR > 1.5, ascites, hepatic encephalopathy, and other organ failure due to DILI; (5) fatal: dies or liver transplantation because of DILI [11].

The definition of hypersensitivity features was positive serum anti-nuclear antibody, anti-mitochondrial antibody, eosinophilia, skin rash or fever [13].

Serum hepatitis B virus (HBV)-DNA was performed using COBAS Taqman HBV test (Roche Molecular Diagnostics, Pleasanton, CA, USA), with the detectable lower limit of 20 IU mL^{-1}.

Statistical analyses

Chi-square test or Fisher's exact test was used to compare the categorical parameters. Also, the Student's *t*-test, the Mann–Whitney test or the Kruskal-Wallis test was performed to compare the continuous parameters between groups. The Wilcoxon signed ranks test was carried out to compare the latency between the first use of statin and rechallenge. Odds ratios (OR) and confidence intervals (CI) were calculated using a logistic regression analysis. The continuous parameters were presented as mean and 95% CI for mean. All of the statistical tests were based on a two-tailed probability and a P value < 0.05 was considered significant. All analyses were performed using the SPSS 17.0 software (SPSS Inc., Chicago, IL, USA).

Results

A total of 108 patients with SILI and 324 controls were enrolled into this study (Table 1). The patients with SILI were older than the controls (66.0 *vs.* 61.7 years old, $P < 0.001$), and with higher percentage of intake of high dose of statin (25.9% *vs.* 16.4%, $P = 0.027$). However, there was no statistical

Table 1

Characteristics of patients with statin-induced liver injury and controls

	Patients (n = 108)	Control (n = 324)	P-value
Sex (M/F)	59/49	165/159	0.578
Age (years)†	66.0 (64.1–68.0)	61.7 (60.7–62.6)	<0.001*
Hepatitis B carrier	16 (14.8%)	44 (13.6%)	0.749
Abnormal baseline liver tests	18 (16.7%)	40 (12.3%)	0.257
Body mass index (>25 kg/m^2)	20 (18.5%)	65 (20.1%)	0.781
Diabetes mellitus	21 (19.4%)	59 (18.2%)	0.776
Habitual alcohol drinking	18 (16.7%)	40 (12.3%)	0.257
eGFR < 60 mL/min/1.73 m^2	29 (26.9%)	76 (23.5%)	0.518
High dose of statin	28 (25.9%)	53 (16.4%)	0.027*
Latency (days)†	60.0 (54.5–65.4)	–	
Peak serum ALT (U/L)†	397.6 (327.6–467.7)	39.3 (37.7–41.0)	<0.001*
Peak serum ALP (U/L)†	240.8 (189.6–292.1)	94.2 (87.6–100.9)	<0.001*
Peak total bilirubin (mg/dL)†	2.78 (1.93–3.65)	0.91 (0.88–0.95)	<0.001*
Type of liver injury (H/M/C)	56/31/21 (51.9%/28.7%/19.4%)	–	
Hypersensitivity features	9 (8.3%)	–	

ALP, alkaline phosphatase; ALT, alanine aminotransferase; C: cholestatic; eGFR, estimated glomerular filtration rate; H, hepatocellular; M, mixed.
*$P < 0.05$. †Data expressed as mean (95% confidence interval for mean). Upper limit of normal value of ALT: 40 U/L, ALP: 100 U/L and total bilirubin: 1.6 mg/dL.

difference between SILI patients and controls in sex, HBV carrier status, abnormal baseline liver biochemical tests, BMI, DM, habitual alcohol drinking and eGFR (Table 1). The mean latency (incubation period) was 60.0 (95% CI: 54.5–65.4) days. Furthermore, there was no predilection of liver injury to the seven available statins. The hepatocellular pattern was the major type of liver injury (51.9%), followed by mixed pattern (28.7%) and cholestatic pattern (19.4%). The mean serum ALT and total bilirubin were 397.6 (327.6–467.7) U L^{-1} and 2.78 (1.93–3.65) mg dL^{-1}, respectively (Table 1). According to the definition of severity by DILIN, 19 (17.6%) patients were categorized as above moderate degree. Among the SILI patients, there was no statistical difference in baseline and peak liver function tests, latency, resolution time and severity between HBV carriers and non-HBV carriers (Table 2). The mean Roussel Uclaf Causality Assessment Method (RUCAM) score was 4.5 (4.1–4.9) in HBV carriers and 7.6 (7.5–7.8) in non-HBV carriers (Table 2). Most of the HBV carriers were categorized as possible DILI, while most of the non-HBV carriers were in the classification of probable DILI.

There was no statistical difference in sex, age, liver function tests, type of liver injury, latency, severity and HBV status among SILI induced by different statins in this study (Table 3).

Multiple logistic regression analysis has shown that high dose of statin and old age were the two independent risk factors of SILI (OR and 95% CI: 1.93, 1.08–3.35, $P = 0.025$, and 1.73, 1.07–2.80, $P = 0.027$, respectively) (Table 4).

Figure 1 shows the management and outcome of patients with SILI. Thirty-four (31.5%) patients can be continuously administered original statin with gradual improvement in liver tests. Thirty-one (28.7%) of patients discontinued statin therapy due to overt SILI without rechallenge with other statins. One 80-year-old male patient with diffuse membranous glomerulonephritis treated with rosuvastatin died of SILI-related sepsis. Forty-three (39.8%) patients with overt SILI were rechallenged with other statins after improvement of liver function. Of those, 19 patients again had overt hepatitis and thereafter had their statin treatment discontinued; the other 24 patients could switch to other statins uneventfully. Finally, 58 (53.7%) patients could be treated with original or another statin safely, while 50 (46.3%) patients failed further statin treatment.

The mean latency period of the second episodes of SILI when rechallenged with other statins was 44.2 (36.3–52.1) days, which was shorted than that of the first episode (66.1 days, $P < 0.001$).

Only three of the 16 HBV carriers had been checked HBV-DNA in 6 months before the administration of statins, and their HBV-DNA were all undetectable. The HBV-DNA was assayed in 12 of these 16 HBV carriers during the episode of liver injury. Undetectable levels were found in nine of them, and lower titres were noted in three, with the levels of 38, 102 and 538 IU mL^{-1}, respectively.

Table 2

Comparisons of statin-induced liver injury between hepatitis B virus (HBV) carrier and non-HBV carriers

	HBV carriers (n = 16)	Non-HBV carriers (n = 92)	P-value
Sex (M/F)	5/11	54/38	0.057
Age (>60 years)	10 (62.5%)	67 (72.8%)	0.388
Abnormal baseline liver tests	5 (31.3%)	13 (14.1%)	0.138
BMI (>25 kg/m^2)	1 (6.3%)	19 (20.7%)	0.296
Diabetes mellitus	3 (18.8%)	18 (19.6%)	1.000
Habitual alcohol drinking	3 (18.8%)	15 (16.3%)	0.728
eGFR < 60 mL/min/1.73 m^2	4 (25%)	25 (27.2%)	1.000
High dose of statin	4 (25%)	24 (26.1%)	1.000
Latency (days)*	61.3 (48.8–73.7)	59.8 (53.7–65.9)	0.823
Peak serum ALT (U/L)*	408.1 (195.8–620.4)	395.7 (320.4–471.1)	0.423
Peak serum ALP (U/L)*	266.5 (152.4–380.7)	236.3 (178.8–293.9)	0.863
Peak total Bilirubin (mg/dL)*	2.14 (1.54–2.75)	2.89 (1.90–3.90)	0.155
Severity (1,2/3,4,5)†	13/3	76/16	1.000
Type of liver injury (H/M/C)	9/1/6	47/30/15	0.038
RUCAM scores*	4.5 (4.1–4.9)	7.6 (7.5–7.8)	<0.001

ALP, alkaline phosphatase; ALT, alanine aminotransferase; C: cholestatic; H, hepatocellular; M, mixed; RUCAM, Roussel Uclaf causality assessment method. *Data expressed as mean (95% confidence interval for mean). †Severity defined by Drug-Induced Liver Injury network (DILIN): 1, mild, 2, moderate, 3, moderate–severe, 4, severe, 5, fatal.

Table 3

Statin-induced liver injury in different statins

	Lovastatin (*n* = 8)	Pravastatin (*n* = 11)	Simvastatin (*n* = 17)	Fluvastatin (*n* = 20)	Atorvastatin (*n* = 16)	Rosuvastatin (*n* = 28)	Pitavastatin (*n* = 8)	*P*
High/low dose	40 mg/20 mg	40 mg/10 mg	40 mg/20 mg	80 mg/20 mg	40 mg/10 mg	10 mg/5 mg	4 mg/2 mg	
No. of high/ low dose	1/7	0/11	3/14	8/12	5/11	8/20	3/5	0.590
Sex (M/F)	4/4	6/5	12/5	7/13	11/5	15/13	4/4	0.391
Age (>60years)	6 (75%)	8 (72.7%)	12 (70.6%)	11 (55.0%)	12 (75%)	21 (75%)	7 (87.5%)	0.679
ALT (U/L)*	283.1 (234.3–331.9)	384.6 (143.5–625.8)	509.2 (136.7–881.8)	348.5 (258.7–438.4)	394.9 (291.5–498.4)	448.6 (324.9–572.4)	242.1 (159.6–324.7)	0.593
ALP (U/L)*	261.2 (29.4–493.2)	222.7 (120.0–325.4)	365.1 (80.0–650.4)	196.7 (127.8–265.6)	176.2 (97.2–255.3)	243.2 (179.6–307.0)	212.1 (76.6–347.7)	0.516
Total bilirubin (mg/dL)*	3.68 (0.23–7.14)	3.66 (0.44–7.76)	5.11 (0.91–9.32)	1.70 (1.22–2.19)	1.78 (1.30–2.27)	2.49 (1.00–3.99)	1.47 (0.95–2.00)	0.234
Type of liver injury (H/M/C)	5/1/2 (8.9%/12.5%/25%)	6/2/3 (10.7%/18.2%/27.3%)	8/4/5 (14.3%/23.5%/29.4%)	12/4/4 (21.4%/20%/20%)	10/5/1 (17.9%/31.3%/6.3%)	12/12/4 (21.4%/42.9%/14.3%)	3/3/2 (5.4%/37.5%/25%)	0.706
Latency (days)*	63.0 (46.5–79.6)	58.0 (43.8–72.2)	54.4 (42.0–66.7)	49.7 (41.6–57.8)	67.3 (55.4–79.2)	69.1 2(52.5–85.7)	50.8 (38.7–62.8)	0.225
Severity† 1/2/3/4/5	5/2/0/1/0	8/2/0/1/0	11/1/1/4/0	15/3/2/0/0	9/3/4/0/0	20/2/4/1/1	7/1/0/0/0	0.393
Hepatitis B carrier	2 (25%)	1 (9.1%)	4 (23.5%)	1 (5.0%)	0 (0%)	6 (21.4%)	2 (25%)	0.245

ALP, alkaline phosphatase; ALT, alanine aminotransferase; C, cholestatic; H, hepatocellular; M, mixed. *Data expressed as mean (95% confidence interval for mean). †Severity defined by Drug-Induced Liver Injury network (DILIN): 1, mild, 2, moderate, 3, moderate–severe, 4, severe, 5, fatal.

Table 4

Multivariate analysis of risk factors for statin-induced liver injury

	Odds ratio	95% CI	*P*-value
High dose of statin	1.93	1.08–3.35	0.025*
Age > 60 years old	1.73	1.07–2.80	0.027*
Chronic hepatitis B infection	1.18	0.62–2.22	0.618
Abnormal baseline liver tests	1.09	0.57–2.10	0.787

CI, confidence interval. *$P < 0.05$

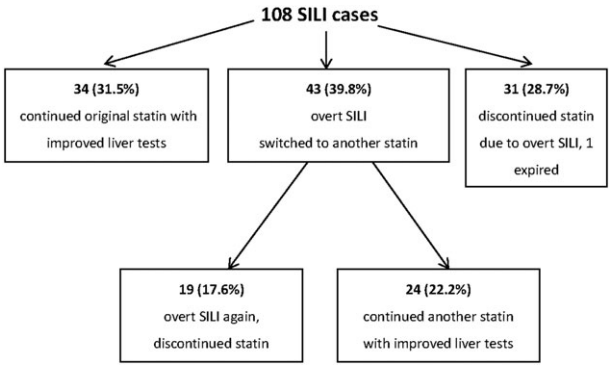

Figure 1

Management and outcome of 108 patients with statin-induced liver injury (SILI)

The anti-hepatitis B core antibody IgM was tested in nine of the 16 HBV carriers, and 41 of the 92 non-HBV carriers; none of them had positive results. The anti-hepatitis C antibody was assayed in all of the included subjects, and none of them was positive. The other hepatitis markers, such as anti-hepatitis A antibody IgM, anti-cytomegalovirus antibody IgM, anti-Epstein–Barr virus antibody IgM and anti-herpes simplex virus antibody IgM had been tested in more than half of the patients, and none of them revealed positive results.

Discussion

Statins are the most commonly prescribed drugs for lowering serum cholesterol and which are always administered lifelong. Therefore, the safety of statins has received much attention. Most of the previous reports concerning hepatotoxicity of statins are based on the studies of Caucasians [1–7]. The present Asian study underlines the safety of statins in chronic hepatitis B carriers, and highlights two susceptibility risk factors of SILI: high dose and old age.

Clinically overt hepatitis due to statins is believed to be rare. It appears that only three cases of SILI were found in Iceland from 2010 to 2011 [1], 22 cases in the US DILIN from 2004 to 2012 [14], 73 cases in the Sweden Adverse Drug Reactions Advisory Committee from 1988 to 2010 [15], and 47 cases in the Spanish Hepatotoxicity Registry (REH) from 1994 to 2012 [16]. However, we collected 108 cases of SILI with clinically significant elevation of liver enzyme tests in 4 years. To our knowledge, this is the largest case series to date. Statins may not be as innocuous as generally believed in Taiwan, given the relatively large number of SILI cases found in such a short time. Moreover, the real number of SILI cases in this study should be more than 108, because many cases were excluded by our strict inclusion and exclusion criteria.

One large population-based cohort study from the UK addressed the possibility that statins may increase the risk of moderate to severe SILI [17]. Furthermore, a recent meta-analysis of 246 955 participants from 135 randomized controlled trials disclosed that statins have a higher risk of transaminase elevation (OR: 1.51, 95% CI: 1.24–1.84) [18]. However, many other studies with different study designs and scales have shown that statins do not increase the risk of significant liver injury [19–23]. According to recent studies and clinical observations, the US Food and Drug Administration (FDA) removed the need for routine periodic monitoring of liver enzymes in patients taking statins on the labels of statins [24]. The labels now recommend that liver enzyme tests should be performed before starting statin therapy, and as clinically indicated thereafter.

A few studies have focused on the safety of statins in patients with chronic liver diseases [2–7]. Chalasani *et al*. first demonstrated that patients with elevated baseline liver enzymes do not have a higher risk of SILI [2, 3]. Khorashadi *et al*. further revealed that statins are associated with a higher incidence of mild to moderate elevation of liver enzymes in patients with chronic hepatitis C, but there was no association of severe SILI and chronic hepatitis C [4]. Many of the subsequent studies also supported the safety of statin in patients with fatty liver diseases and chronic hepatitis C [5–7].

Chronic hepatitis B is prevalent in Asia, South Africa and many other areas. Evidence has showed that CHBI may increase the incidence and severity of DILI from anti-tuberculosis drugs [8–10]. It is reasonable to suspect the impact of CHBI on SILI. However, almost all the previous relevant studies were focused on patients with hepatitis C and fatty liver diseases. Only one brief report with very limited cases from China suggested that the incidence of SILI was similar between HBV carriers and non-HBV carriers; but the HBV carriers had a significantly increased change in serum ALT levels from baseline compared with those of non-HBV carriers [25]. However, our study could not demonstrate the association of CHBI and SILI, both in incidence and severity of hepatotoxicity (Table 2), which underscores the safety of statin therapy in HBV carriers.

Statin-induced elevation of liver enzyme tests usually occur within the first 3–12 months subsequent to the introduction of therapy [14–16]. The median latency to onset of liver injury was 155 days in the US DILIN [14], 3 months in a Swedish study [15] and 57 days in Spanish REH [16]. The median latency of the present study (56 days) is shorter than that in the US and Swedish studies [14, 15], but similar to that in the Spanish data [16]. Whether Asians and Caucasians have different susceptibility to the accumulated toxic metabolites of statins is open to debate. Nevertheless, we did not find any statistical difference in latency between HBV carriers and non-HBV carriers.

Although a few studies challenged the relationship of dose and SILI [26], most studies have demonstrated that using a higher dose of statin can easily induce liver injury [23, 27, 28]. Our study also validated that dose is a risk factor of SILI. Whether monitoring liver function in patients taking a high dose of statins is cost-beneficial warrants further prospective studies.

In this study we also found that old age may increase the risk of SILI, which was consistent with the finding of Spanish REH [16]. It is speculated that the elderly tend to have higher serum cholesterol level and need a higher dose of statin to achieve the therapeutic goal. In addition to the low disposition ability of drug metabolites, comorbidity may increase the risk of SILI in the elderly. Age was also found to be associated with hepatotoxicity induced by other drugs [29].

Although the outcome data of SILI is sparse, it is generally believed that elevations of liver tests in most SILI cases are transient, asymptomatic and may resolve even with continuation of the same statin without dose adjustment [30]. However, continuous administration of the same drug to induce DILI is potentially grave, and is not recommended as a general rule.

From the clinical viewpoint, rechallenge is rarely performed because of ethical concerns. Acute liver failure may happen due to rechallenge, especially in hepatocellular-type DILI. Rechallenge is acceptable only if the drug is deemed essential and unalterable, such as anti-tuberculosis drugs. But only some of the patients rechallenged with anti-tuberculosis drugs can tolerate the drugs safely [8, 9]. In the present study, 43 of the 108 patients with SILI were rechallenged with other statins after recovery of liver function, owing to the clinical need of statins. However, 19 of the 43 patients had overt liver injury again. It seems that the statins have class effect in liver injury, and rechallenge with statins is discouraged in patients with overt SILI.

Concerning the predilection of liver injury in different statins, rosuvastatin, fluvastatin or atorvastatin have been mentioned to have higher risk of SILI in various studies [16, 17, 20, 23]. However, the present study and many other studies cannot demonstrate any statistical difference in SILI among various statins [31, 32]. One possibility is the relatively small number of SILI cases in our and other studies, which hinders the capacity to reach statistical significance. The other possibility is that all the statins have a similar class effect.

Only 8.3% (9/108) of our series exhibited hypersensitivity, which was lower than the 36% in a Spanish study [16] and the 27.3% in the US study [14]. The ethnic difference between Asians and Caucasians may affect the presentation of hypersensitivity features. However, the SILI patients with characteristics of hypersensitivity may be underestimated in our study, because this is a retrospective study.

The limitation of this study is that this is a single-centre retrospective case–control study. Owing to the low incidence of SILI, a case–control model was used in this study. Therefore, we cannot calculate the incidence of SILI in total or individual statins. The other limitation is that HBV-DNA and other viral hepatitis markers were not performed in all patients. Some of the episodes of liver dysfunction may be due to a flare-up of hepatitis B or other viruses.

In conclusion, the current study found that high doses of statin and old age are susceptibility risk factors of SILI. Hepatitis B carriers and patients with abnormal baseline liver tests do not have higher risks of SILI. We still need to be vigilant about the occurrence of SILI, because nearly half of SILI cases in this study were discontinued statin treatment due to severe hepatotoxicity.

Competing Interests

The authors declare no conflict of interest and confirm to have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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Contributors

LYW, YSH, CLP, BH and HCL contributed substantially to the conception and design of the work. All authors made contributions to the acquisition, analysis or interpretation of data. LYW and YSH contributed equally to this work. LYW and YSH drafted the paper and all authors revised it critically for important intellectual content and gave their final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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